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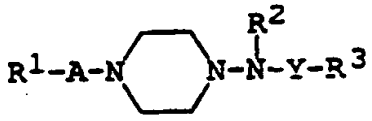
(54) Title: NEW USE OF AMINOPIPERAZINE DERIVATIVES

(57) Abstract

This invention relates to the use of a compound of formula (I) wherein each symbol is as defined in the description, or its pharmaceutically acceptable salt, for treating and/or preventing schizophrenia, depression, stroke, and the like.



(I)

DESCRIPTION

NEW USE OF AMINOPIPERAZINE DERIVATIVES

TECHNICAL FIELD

This invention relates to a new use of aminopiperazine derivatives and pharmaceutically acceptable salts thereof for the treatment and/or prevention of schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism in mammals.

BACKGROUND ART

The aminopiperazine derivatives used in this invention are known as described in PCT International Publication No. WO 91/01979 that said aminopiperazine derivatives possess the potentiation of the cholinergic activity and are useful in the treatment of disorders in the central nervous system for human beings, and more particularly in the treatment of amnesia, dementia, senile dementia and the like.

DISCLOSURE OF INVENTION

The present invention relates to a new use of aminopiperazine derivatives and pharmaceutically acceptable salts thereof for the treatment and/or prevention of schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism for mammals.

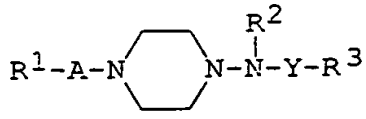
Accordingly, this invention is to provide a new use of aminopiperazine derivatives and pharmaceutically acceptable salts thereof for treating and/or preventing schizophrenia,

depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism.

Further, this invention is to provide an agent and a pharmaceutical composition for treating and/or preventing schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism, which comprises said aminopiperazine derivatives and pharmaceutically acceptable salt thereof.

Still further, this invention is to provide a therapeutic method for the treatment and/or prevention of schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism, which comprises administering said aminopiperazine derivatives and pharmaceutically acceptable salts thereof to mammals.

The aminopiperazine derivatives used in this invention can be represented by the following general formula [I] :



[I]

wherein R^1 is lower alkyl, aryl, ar(lower)alkoxy or a heterocyclic group, each of which may be substituted with halogen,

R^2 is hydrogen or lower alkyl,

R^3 is cyclo(lower)alkyl, aryl or ar(lower)alkyl, each of which may be substituted with halogen,

A is $-\overset{O}{\overset{\|}{C}}-$, $-SO_2-$ or lower alkylene, and

Y is $-\overset{O}{\overset{\|}{C}}-$, $-SO_2-$ or $-\overset{O}{\overset{\|}{C}}NH-$,

and pharmaceutically acceptable salts thereof.

Said compound (I) and pharmaceutically acceptable salts thereof are useful in the treatment and/or prevention of schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism in mammals.

Particulars of the various definitions mentioned in this specification and preferred examples thereof are explained in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, or the like, in which preferable one is methyl.

Suitable "aryl" may be phenyl, naphthyl, tolyl, xylyl, mesityl, cumenyl, and the like, in which preferable one is phenyl or naphthyl.

Suitable "ar(lower)alkoxy" may be benzyloxy, phenethyloxy, phenylpropoxy, benzhydryloxy, trityloxy and the like.

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic one containing at least one hetero atom such as nitrogen atom, oxygen atom or sulfur atom.

The preferred examples of thus defined "heterocyclic group" may be an unsaturated, 3 to 8-membered, more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridyl N-oxide, dihydropyridyl, tetrahydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazinyl, tetrazolyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl, etc.;

saturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholino, sydnonyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonoyclcic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated, condensed heterocyclic group containing 1

to 2 sulfur atom(s), for example, benzothienyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s), for example, benzofuranyl, etc.; or the like.

Suitable "cyclo(lower)alkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

Suitable "ar(lower)alkyl" may be benzyl, phenethyl, phenylpropyl, benzhydryl, trityl, and the like.

Suitable "lower alkylene" may be methylene, ethylene, propylene, pentamethylene, hexamethylene, and the like.

The above-mentioned "lower alkyl", "aryl", "ar(lower)alkoxy", "heterocyclic group", "cyclo(lower)alkyl" and "ar(lower)alkyl" may be substituted with halogen [e.g. fluorine, chlorine, bromine and iodine].

Preferred compound [I] is one which has a lower alkyl, phenyl, naphthyl or thienyl for R^1, hydrogen or lower alkyl for R^2, phenyl which may be substituted with a halogen for R^3, $-\overset{O}{\overset{\|}{C}}-$ for A, and $-\overset{O}{\overset{\|}{C}}-$ or $-SO_2-$ for Y.

More preferred compound [I] is one which has a lower alkyl for R^1, hydrogen for R^2, phenyl which is substituted with a halogen for R^3, $-\overset{O}{\overset{\|}{C}}-$ for A, and $-\overset{O}{\overset{\|}{C}}-$ for Y.

Most preferred compound [I] is N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide.

Suitable pharmaceutically acceptable salts of the compound [I] are conventional non-toxic salts and include acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate,

benzenesulfonate, toluenesulfonate, etc.], a salt with an amino acid [e.g. aspartic acid salt, glutamic acid, salt, etc.] and the like.

It is to be noted that the compound [I] may include one or more stereoisomer(s) due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

Additionally, it is to be noted that any hydrate of the compound [I] is also included within the scope of this invention.

Now in order to show the utility of the compound [I] and pharmaceutically acceptable salts thereof in this invention, the pharmacological test was carried out and its abstract is shown in the following.

The effect of the compound [I] upon cognitive function was examined using an operant delayed non-match to place paradigm (DNMTP) task which is shown to be disrupted dose-dependently by the administration of haloperidol. The following interactions were explored: haloperidol plus amphetamine, haloperidol plus the compound [I] and haloperidol plus the compound [I] and amphetamine. Neither a low dose of amphetamine nor two doses of the compound [I] when administered with haloperidol, or alone, altered the profile of performance relative to control. The experiments with haloperidol and the compound [I] plus amphetamine revealed a profound attenuation of the deficits associated with incerasing doses of haloperidol by the larger dose of the compound [I].

These expeiments confirmed that the compound [I] has a specific effect on dopaminergic status which appears to be state dependent and is useful for treating and/or preventing schizophrenia, depression, stroke, head injury, nicotine

withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism.

For therapeutic purpose, the compound [I] and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral or parenteral administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound [I] will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Examples is given for the purpose of illustrating this invention.

Example 1

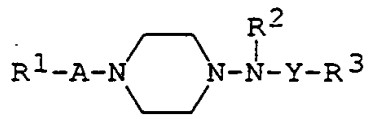
(Capsule)

N-(4-Acetyl-1-piperazinyl)-4-fluorobenzamide	5 mg
Lactose	80 mg

The above-mentioned ingredients were mixed and the mixture was encapsulated to provide the capsule.

CLAIMS

1. Use of a compound of the formula :



[I]

wherein R^1 is lower alkyl, aryl, ar(lower)alkoxy or a heterocyclic group, each of which may be substituted with halogen,

R^2 is hydrogen or lower alkyl,

R^3 is cyclo(lower)alkyl, aryl or ar(lower)alkyl, each of which may be substituted with halogen,

A is $-\overset{O}{\overset{\|}{C}}-$, $-SO_2-$ or lower alkylene, and

Y is $-\overset{O}{\overset{\|}{C}}-$, $-SO_2-$ or $-\overset{O}{\overset{\|}{C}}NH-$,

or its pharmaceutically acceptable salt for treating and/or preventing schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism.

2. A use of the compound defined in Claim 1 as an agent for treating and/or preventing schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity

disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism.

3. An agent for treating and/or preventing schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism, which comprises the compound defined in Claim 1.

4. A method for treating and/or preventing schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism, which comprises administering the compound defined in Claim 1 to mammals.

5. A use of the compound defined in Claim 1 for manufacturing a medicament for treating and/or preventing schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism.

6. A pharmaceutical composition for treating and/or preventing schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's

disease or autism, which comprises the compound defined in Claim 1 in admixture with a carrier or excipient.

7. A process for preparing the pharmaceutical composition of Claim 6, which is characterized by admixing the compound with a carrier or excipient.